REMARKS

The Examiner's Answer of July 21, 2011, has been carefully studied. Claims 13 and 20 currently appear in this application. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration and formal allowance of the claims.

Claim Amendments

Claims 10, 12, 14 and 17-19 have been cancelled. New claim 20 has been submitted.

New claim 20 replaces claim 12. The term "under shading" in new claim 20 is supported in the specification as filed at paragraph [0055], "The capsules were sealed with gelatin and left for 53 days under 40°C/75% RH and shading." The paragraph as a whole shows the formation of (5E,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, the trains form of ED-71, in an oily preparation, which was prepared by dissolving (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol from (5Z,7E)-(1R,2R,3R)-2-(3-hydroxypropoxy)-9,10-secocholesta-5,7,10(19)-triene-1,3,25-triol, ED-71, in MCT and was left under shading, i.e., shaded from exposure to light.

Rejections under 35 U.S.C. 112

Claim 18 is rejected under 35 U.S.C. 112, fist paragraph, as failing to comply with the written description requirement. Claim 18 is also rejected under 35 U.S.C. 112, second paragraph, for being indefinite.

As the present amendment cancels claim 18, these rejections are now moot.

Art Rejections

Claims 10-, 14, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Yamauchi et al., US 6,448,421.

As the present amendment cancels claims 10, 14, 17 and 18, this rejection is now moot.

Claims 10, 14, 17 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Miyamoto et al., *Chem. Pharm. Bull.* and Miyamoto et al., US 4,666,634.

As the present amendment cancels claims 10, 14, 17 and 18, this rejection is now moot.

Claims 10, 12-14, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamauchi, Miyamoto, JP 05-004925 and Chen et al., WO 03/047595.

As the present amendment cancels claims 10, 14, 17 and 18, this rejection with respect to claims 10, 14, 17 and 18 is now moot.

Submitted herewith is a copy of Malatesta et al., *J.A.C.S.*, 1981, **103**:6781-6783, which shows, in Figure 1, that the conversion of 7-DHC (vitamin D_3) to 5-6 trans D_3 (the trans form of vitamin D_3) is driven by irradiation. This indicates that light is essential to the formation of the trans-form of vitamin D_3. This is also indicated in Scheme I of Yamada et al., *J. Org. Chem.*, **48(20)**, 1983, 3477-3483, a copy of which is submitted herewith.

However, the present inventors have discovered that the trans form of ED-71 is formed from ED-71 **without exposure to light**. Accordingly, the presently claimed method for suppressing the formation of the trans form of ED-71 was predicated on the discovery that the trans form of ED-71 is formed even in the absence of exposure to light, that is, under shading.

Yamaguchi discloses in columns 11 and 12 that the pro form (2) of ED-71 is first converted to the pre form of ED-71 and then to ED-71 by heating and irradiation with ultraviolet light, Yamaguchi also discloses, in columns 13 and 14, that some analogues are formed during the photo and thermal isomerization reactions, including lumi and tachy forms of ED-71, which were isolated. However, Yamaguchi is silent with respect to the formation of the trans form of ED-71.

Regarding the relationship between the conversion of the pro form of vitamin D_3 to vitamin D_3 via the pre form of vitamin D_3 and the formation of the trans form of vitamin D_3, Malatesta mentioned above also provide Figure 1, which shows the conversion of the pro form (7-DHC E) to the vitamin D_3 via the pre form (P_3) is shown to be independent from the formation of the trans form of vitamin D_3 (5,6-trans D_3) from the vitamin D_3 (7-DHC). It is clear from Figure 1 that the trans

form is formed **only** from irradiating vitamin D_3. In other words, the trans form is not formed form the pro form or the pre form other than via vitamin D_3.

It is clear from the above that one skilled in the art, during the photo and thermal isomerization reactions disclosed in Yamauchi, that the trans form of vitamin D_3 would not be directly formed from the pro form or from the pre form, and that Yamauchi merely discloses that the pro form of ED-71 is converted to ED-71 via the pre form of ED-71. As stated above, Yamauchi is silent with respect to the formation of the trans form of ED-71.

Therefore, although Yamauchi discloses isolation of some analogues, including the lumi and tachy forms of ED-71, one skilled in the art would not have expected from the Yamauchi disclosure that the trans form of ED-71 would be formed from the pro form or the pre form of ED-71 rather than via ED-71.

Miyamoto'634 teaches in column 2 a compound of formula (I) which is a Diels-Alder adduct and which is provided for the formation of formula (II), which is also a Diels-Alder adduct having an R'O substituent at the 2-position. Miyamoto'634 specifically discloses at column 5 that the Diels-Alder adduct of 2β-methoxy-5,7-cholestadiene-1α,3β-diol, a compound of formula (II), is converted to 2β-methoxy-5,7-cholestadiene-1α,3β-diol by reaction with lithium aluminum hydride, and that the resulting product, 2β-methoxy-5,7-cholestadiene-1α,3β-diol, is then converted to 1α-hydroxy-2β-methoxy vitamin D_3, which is a vitamin D_3 having a methoxy substituent in the 2β-position, by irradiation and heating. As with Yamauchi, Miyamoto'634 is silent with respect to the formation of the trans form of vitamin D_3.

Since the Diels-Alder adducts of formulae (I) and (II) are prepared merely for the introduction of a 2β-substituent into vitamin D_3, they are not considered to be involved in the isomerization of vitamin D_3. In Miyamoto'634, only the reaction in which 2β-methoxy-5,6-cholestadiene-1α,3β-diiol is converted to vitamin D_3 by irradiation and heating should be taken into consideration as reactions involved in isomerization of vitamin D_3.

It should be noted that 1β-methoxy-5,7-cholestadiene-1α,3β-diol is the pro form of vitamin D_3. Thus, Miyamoto'634 substantially discloses only the conversion of the pro form of bi vitamin D_3 to the corresponding vitamin D_3 by irradiation and heating, which are not reactions involved in isomerization of D_3. The reactions are substantially the same as the photo and thermal isomerization reactions disclosed in Yamauchi.

The disclosures of Miyamoto in *Chem. Pharm. Bull.* are substantially the same in Miyamoto'634.

Thus, one skilled in the art would also not have expected from the disclosure of either Miyamoto reference that the trans form of vitamin D_3 is formed from the corresponding pro form other than via vitamin D_3.

In summary, the method of claim 20, which was derived from claim 12, is characterized in that the trans form of ED-71 is formed from ED-71 in an oily preparation maintained under shading (i.e., in the absence of light). Yamauchi discloses the photo and thermal isomerization reactions in which the pro form of ED-71 is converted top ED-71 via the corresponding pre form by irradiating with UV

light and heating. Yamauchi also discloses the isolation of some analogues formed during the reactions. However, in view of the disclosures of Malatesta showing that the conversion of the pro form to vitamin D_3 via the pre form, is independent from the formation of the trans form from of vitamin D_3. One skilled in the art would not have expected from Yamauchi that the trans form of ED-71 would be formed from the pro form or the pre form of ED-71 other than via ED-71. The Miyamoto disclosures are substantially the same as Yamauchi. Thus, one skilled in the art would not have expected from these references that the trans form of ED-71 would be formed from the pro form or the pre form of ED-71 other than via ED-71.

Additionally, as noted above, the three cited references are silent with respect to the formation of the trans form of ED-71 or vitamin D_3 from the corresponding vitamin.

Therefore, one skilled in the art would neither have expected from the three prior art references that the trans form of ED-71 is would be formed from the pro form or the pre form of ED-71 other than via ED-71, nor that the trans form would be formed from ED-71 under shading, i.e., in the absence of light.

Chen discloses a pharmaceutical composition comprising an active vitamin D may further includes α-tocopherol. However, it neither discloses that the active vitamin D is isomerized to the corresponding trans form under shading nor that α-tocopherol suppresses isomerization. It would be impossible to conclude that such a pharmaceutical composition suggests the method of suppressing the formation of the trans form of ED-71 as claimed herein merely by adding α-tocopherol.

JP 05-004925 and JP 06-087750, disclose the use of tocopherol for stabilizing a pharmaceutical composition or soft capsules comprising vitamin D, respectively. However, like Chen, they neither discloses isomerization of vitamin D to the corresponding trans form under shading, nor suppression of the isomerization with α-tocopherol. Therefore, these publications add nothing to the Yamauchi or Miyamoto references in preventing isomerization of ED-71 to the trans form under shading.

It is clear that none of the art cited has anything to do with preventing isomerization of ED-71 to the trans form under shading, either with or without the presence of dl-α-tocopherol.

Regarding the STN registries referred to on pages 10-11 of the Examiner's Answer, only RN 861996-34-1 relates to the trans form of ED-71. However, in the registry, ED (entered date) is shown to be August 2005, which is after the international filing date of the present application, i.e., February 7, 2005. Therefore, the registries should not be considered prior art under 35 U.S.C. 102(a) or 103(a).

Regarding the Examiner's statement relating to the differences in structure between the trans form of ED-71 an ED-71 at page 18 of the Examiner's Answer, it should be noted that, although the difference in structure is small, it may provide a great difference in properties between the compounds. For example, fumaric acid, which is the trans form of maleic acid, has a melting point of 200°C, while maleic acid has a melting point of 131°C. This is one example of a small

structural difference making a significant difference in properties of the molecules. Therefore, the trans form of ED-71 is not the same as ED-71, and it is in error to regard the herein claimed method as being obvious.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

Respectfully submitted,

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